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An Exposome Perspective to Environmental Enteric Dysfunction

Job O. Mapesa[1,2], Amy L. Maxwell[1,3], and Elizabeth P. Ryan[1]

[1]Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, Colorado, USA; [2]Department of Public Health and Human Nutrition and Dietetics, Kenya Methodist University, Nairobi, Kenya; [3]Department of Health Sciences, University of Alaska Anchorage, Alaska, USA

Address correspondence to Elizabeth P. Ryan, Department of Environmental and Radiological Health Sciences, 200 W. Lake St., 1680 Campus Delivery, Fort Collins, CO 80523-1680 USA. Telephone: (970) 491-1536. E-mail: E.P.Ryan@colostate.edu

Running title: Role of exposome in enteric dysfunction

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Abstract

Background: Environmental exposures to chemicals have been shown to influence gastrointestinal function, yet little is known regarding whether chemical mixtures may be involved in the development of a subclinical enteric dysfunction found in infants and children born into poor hygiene and sanitation. Advances in gastrointestinal and immunotoxicology fields merit inclusion in complex discussions of environmental enteric dysfunction (EED) that severely impact children in developing countries.

Objective: To highlight exposome approaches for investigating the potential influence of environmental chemical exposures on EED development, including a role for toxicant modulation of gut immune system and microbiome function.

Discussion: A major focus on fecal-oral contamination in impoverished living conditions already exists for EED, and should now expand to include environmental chemicals such as pesticides and heavy metals that may be anthropogenic, dietary or from microbial sources. A comprehensive characterization of environmental chemical exposures prenatally and occurring in infants and young children will enhance our knowledge of any associated risks for EED and stunting.

Conclusions: Integrating EED, chemical exposure, and stunting at various ages during childhood will enhance our apparent limited view when evaluating EED. Etiology and intervention studies should evaluate the suite of environmental chemical exposures as candidates in the composite of EED biomarkers.

Introduction

Environmental enteropathy (EE) and environmental enteric dysfunction (EED) are terms used to describe the same pathophysiological, subclinical condition of reduced small intestinal barrier and absorptive function that has high prevalence amongst children living in low-middle income countries where poor hygiene and inadequate sanitation and malnutrition pervade (Crane et al. 2015; Keusch et al. 2013). The spectrum of EED involves structural and functional changes to the gastrointestinal tract (GI) that may include, but not be limited to altered villous architecture, impaired mucosal immunity, nutrient malabsorption, and growth faltering (Lin et al. 2013; Lindenbaum et al. 1972). Chronic enteric pathogen exposures, including asymptomatic infections, and intestinal permeability in young children has thus far been central to EED research (Salazar-Lindo et al. 2004). However, we put forth that the role for a diversity of environmental toxicant exposures as well as dysbiosis of the gut microbiome from birth to two years of age represent major gaps in our knowledge of EED. The host burden and the host responses to toxicant exposures were highlighted in the concept of an "enteric dysfunction exposome" (Vrijheid et al. 2014). Across global geography and age groups, EED may be influenced in ways that have not yet been connected to existing knowledge of toxicologic importance, and this commentary highlights the compelling case for xenobiotics to be investigated in EED etiology. As such, the enteric dysfunction exposome would not be limited to enteric pathogens and mycotoxins, but will encompass chemical classes for a wide range of environmental toxicants (i.e. endocrine disrupters, trace heavy metals, persistent organic pollutants (POPs), volatile organic chemicals (VOCs) and behaviors (Miller and Jones 2014). The presence of chemical exposures in maternal blood and breast milk may affect infant immune tolerance, gut microbiome colonization, small intestinal development and nutrient availability

and absorption during in-utero, prenatal and postnatal periods, yet these factors remain poorly characterized in EED endemic regions (Crane et al. 2015; Gordon et al. 2012; Rappaport et al. 2014; Vrijheid et al. 2014). Thus, EED evaluation should include xenobiotic exposures that can be monitored non-invasively through blood, urine, saliva and/or stool using both non-targeted omics-based and targeted measurements of exogenous and endogenous small molecules (Keusch et al. 2014). This approach exhibits strong potential to not only identify a suite of reliable EED exposure biomarkers but also design interventions that can perturb an EED susceptible exposome (Rappaport and Smith 2010; Rappaport 2011; Vrijheid et al. 2014).

Studies in Bangladesh (Lin et al. 2013), Brazil (dos Reis et al. 2007), The Gambia (Campbell et al. 2003; Campbell et al. 2004), Nepal (Langford et al. 2011), Malawi (Agapova et al. 2013; Galpin et al. 2005) and Tanzania (Mduma et al. 2014), demonstrate that EED is widespread and pervasive. The current list of EED associated morbidities provides strong rationale for identifying biomarkers, diagnostics, preventive agents and sustainable treatment solutions (Keusch et al. 2014). Along with prevalent severe acute malnutrition and under-nutrition related childhood mortalities, stunting is postulated to be secondary to EED (Keusch et al. 2013), and may affect multiple generations of the 171 million children affected by stunting globally (de Onis et al. 2013). In a case controlled study of 202 stunted Zimbabwean infants, a measurement of the biomarkers of intestinal inflammation revealed that exposure to low grade, chronic inflammation in-utero and during early postnatal phases of life was associated with stunting likely due to extensive enteropathy that occurs during infancy (Prendergast et al. 2014). We put forward that the milieu of EED causative agents, epigenetic, and genetic factors merit elucidation in order to fill the gap in our knowledge regarding when and how EED can be controlled or prevented. As such, it can be hypothesized that multiple layers of environmental,

microbiological, pharmacological, and dietary interventions are needed to reasonably reduce EED prevalence. Identification of EED biomarkers is the subject of ongoing global health research, and as such opens opportunities for new diagnostics and therapeutics (Mbuya and Humphrey 2015; Prendergast et al. 2015). The nature of EED research in children of developing countries merits inclusion of the spectrum of host-microbe interactions and chemical exposure diversity; investigating the combined effect could advance EED risk assessment, improve EED diagnostics and therapeutics, and deploy EED prevention initiatives.

EED Characteristics, Etiology and Epidemiology

EED is a subclinical disorder characterized by abnormal morphology and physiology of the small bowel; specifically, it features increased gut permeability, altered gut villous architecture and function, nutrient malabsorption, and growth faltering (Lin et al. 2013; Lindenbaum et al. 1972; Prendergast and Kelly 2012). Gastrointestinal tissue biopsies of children with EED display crypt hyperplasia, villous atrophy, lymphocyte infiltration into the lamina propria and epithelium, and reduced mucosal surface area (Lin et al. 2013). The biopsies are also characterized by T-cell activation and heightened Th-1 cellular immune responses similar to what is seen in celiac sprue. This is not consistent with allergic responses, but rather appears to be a response to specific pathogens, presumably from ingestion of food and water containing fecal contaminants (Campbell et al. 2003). The intestinal epithelium creates a physical barrier between the external and internal environments in which the intracellular tight junctions and the apical brush borders prevent microbial attachment and invasion (Shen and Turner 2006). EED develops and occurs in the absence of overt manifestation of diarrhea and was originally referred to as tropical enteropathy in the 1970s when a moderate number of documented cases of abnormal jejunal biopsies were identified from persons in tropical regions (Lindenbaum et al.

1972). Intestinal pathology varied geographically, and the condition resolved when affected individuals migrated to developed regions (Lindenbaum 1973). Subsequent studies in varied populations around the world showed that tropical enteropathy did in fact exist throughout the tropics, but that it was also absent in some tropical populations of high socio-economic status, such as Qatar and Singapore. This illuminated the premise that environmental conditions were critical drivers of the condition as opposed to geographical position (Prendergast and Kelly 2012). We believe that the unsanitary conditions in which EED affected individuals reside contribute to the overriding causal factors of EED. However, we postulate that multiple sources of exposures contribute to both the transient and chronic/persistent nature of EED (Figure 1). In addition to poor sanitation, dietary contaminants and environmental toxicants can be equally hazardous or exert additive and or synergistic effects on the developing gastrointestinal tract via the microbiome, and thus merit qualitative and quantitative assessments for contributions to EED (Breton et al. 2013; De Filippo et al. 2010; Zhang et al. 2015). While EED has been shown to be reversible if acquired in adulthood, as in the adult Peace Corps volunteers study (Lindenbaum et al. 1972), adults who resided in impoverished areas for the duration of their lifetimes demonstrate that EED acquired in childhood is chronic and difficult to reverse even after relocating to clean environments (Kelly et al. 2004; Keusch et al. 2013). For example, in a longitudinal cohort study of healthy African adults in Zambia, endoscopic biopsies of the proximal jejunem were obtained serially over three years to assess for changes in mucosal architecture in response to environmental conditions. At baseline, and over the duration of the study, the entire cohort revealed the absence of predominant finger-like villi, an abnormal biopsy finding representative of EED, even though these adults were “healthy” and asymptomatic of intestinal infection (Kelly et al. 2004).

Microbial and Dietary Origins of EED

Metagenomic studies of infant and childhood stool samples show that early postnatal environmental exposures have a pivotal role in shaping the predominant phylogenic structure of gut microbiota, and that this microbial configuration occurs rapidly during the first two years of life (Kau et al. 2011; Koenig et al. 2011). In a recent Global Enteric Multicenter Study (GEMS) of diarrhea in young children in Mali, The Gambia, Kenya and Bangladesh, it was reported that during the first year of life, a healthy infant gut microbiota is characterized by a comparatively low diversity as well as a relatively high proportion of facultative anaerobes, and potentially pathogenic organisms that are believed to play a role in the development of host immune system. A high throughput 16S rRNA gene sequencing was used to compare fecal microbiota composition in 992 children under five years of age who had been diagnosed with moderate to severe diarrhea with the microbiota from diarrhea-free controls subjects (Pop et al. 2014). Predominant bacteria vary among different populations of children, possibly in relation to diet (De Filippo et al. 2010; Pop et al. 2014; Wu et al. 2011; Yatsunenko et al. 2012). According to Subramanian and colleagues, gut microbiota immaturity was defined by relative microbiota diversity and microbiota-for-age Z score indices. In addition to detecting limited changes in malnourished children split into two dietary treatments, they reported reduced bacterial diversity with detection of 220 significantly different operational taxonomic units, 165 of which had diminished proportional representation in the stool microbiota of severely malnourished children compared to healthy children (Subramanian et al. 2014). Thus, the possible role for an immature gut microbiota associated with low-dose toxicant exposures in EED merits continued investigation (Hall et al. 2007; Subramanian et al. 2014) as the acquisition and composition of gut microbiota has also shown dependence on many factors including region of birth, history of

hospitalization, mode of delivery, infant weaning, diet, age, gender, presence of siblings, infections and antibiotic use (Miller and Jones 2014; Rappaport 2011; Vrijheid et al. 2014; Yatsunenko et al. 2012). It is plausible that EED may cause zinc deficiency by reducing its absorption, yet enteric infections can impair zinc homeostasis, increase deficiency, and aggravate EED by weakening gut barrier functions, which elevates incidences of GI tract infection and inflammation as a result of decreased gut absorptive capacity (Lindenmayer et al. 2014). Chronic parasitic infections with *ascaris*, hookworms, and *trichuris* may trigger or perpetuate EED via multiple inflammatory pathways (Bartelt et al. 2013).

Understanding EED as a congregation of changes in small intestinal function can help prevent malnutrition and stunting in infants in developing countries (Keusch et al. 2013). EED development has been associated with unrestrained enteric T-cell activation by persistent and abnormal concentrations of ingested fecal bacteria in the small intestinal lumen (Humphrey 2009). During nutrient processing, commensal bacteria secrete antimicrobial compounds that prevent infections by pathogenic microbes, and commensals support immune system functions to achieve homeostasis (Caricilli et al. 2014). It has been proposed that disruption of the gut homeostatic balance in children living in pathogen-laden environments supports low-grade chronic immune system stimulation that can culminate into small intestine-function impairment (Ngure et al. 2014). We propose that chemical toxicant exposures merit investigation alongside these pathogens as contributors to low-grade chronic immune stimulation.

The Exposome

Applying an exposome lens to enhance the current understanding of EED may have advantages given the strong evidence already linking dietary exposures, malnutrition, immature gut

microbiota and diarrheal disease-causing pathogens (Salazar-Lindo et al. 2004). The exposome is defined as 'the cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, and behavior' (Miller and Jones 2014). The exposome includes relevant exposures from food, breast milk, water, air and soil, as well as microbes (bacteria, fungus, yeasts, archaea etc.), toxicants and food allergens (Lioy and Rappaport 2011). By evaluating the entire exposome in relation to EED, we may identify missing links in the multiple causative factors that contribute to EED. The exposome integrates overlapping domains of general and specific external factors along with the internal environment of the host (Caricilli et al. 2014). The exposome seeks to enumerate all of the possible sources of exposure, integrate biological data (Lioy and Rappaport 2011; Rappaport 2012), and would incorporate a more holistic picture of environmental exposures to EED epidemiological studies.

Chemical toxicants and gut microbiome studies have revealed meaningful interactions. For example, non-absorbed heavy metals have a direct impact on the gut microbiota (Breton et al. 2013). We postulate that dietary exposure from breast milk, food and water to multiple classes of pesticides might be a major contributor to EED. Children are uniquely sensitive to toxic chemicals in the environment with greater concentrations of exposure to toxicants with respect to their body weight. More studies are needed to understand the interaction between the gut microbiome and xenobiotics in EED-prone regions given that xenobiotics affect physiology, metabolism and gene expression of the human gut microbiome (Maurice et al. 2013).

Mycotoxins are common contaminants in foods such as maize, oats, rye, barley, wheat, and peanuts. An impaired intestinal integrity similar to EED has been demonstrated in animal model

experiments following aflatoxin poisoning (Prendergast and Kelly 2012). Aflatoxin, fumonisin, and deoxynivalenol may have similar EED characteristics by which they impair the gut to induce stunting (Smith et al. 2012). These mycotoxins may also share a convergent pathway resulting in mucosal changes seen in EED (Smith et al. 2012). Specifically, it has been proposed that aflatoxins may affect child growth by collectively reducing zinc bioavailability, impairing protein synthesis and nutrient metabolism in addition to damaging the enterocytes. Sequential insults by these mycotoxins in combination with chemical toxicants may affect children at their most vulnerable developmental stages and serially interrupt critical developmental milestones (Bartelt et al. 2013).

The gut microbiome is central to growth and nutritional status through nutrient transformation as well as immune system and metabolic signaling (Jones et al. 2014). A diminished mucosal surface area and damage to the epithelium may impede nutrient absorption and lead to malnutrition. For instance, abberations in the gut microbiome have been implicated as casual factors in Kwashiorkor, a form of severe acute malnutrition resulting from inadequate nutrient intake in addition to environmental factors (Smith et al. 2013). Early life functional changes in the GI tract may herald, and be exacerbated by myriad of malnutrition drivers including inadequate diet, poverty, food insecurity, and infection with enteric pathogens, culminating in stunting (Keusch et al. 2014).

The microbiome produces many metabolites that greatly influence host response as seen in vitamin and amino acid nutrient processing during infancy (Yatsunenko et al. 2012). Related faulty nutrient processing has been implicated in malnutrition, which subsequently increases susceptibility to infectious diseases (Dorrestein et al. 2014). Research shows that dietary habits

shape nutrigenomics in an evolutionary fashion via influences from human genetics and gut microbiota (Daniell and Ryan 2012), and that systematic changes in dietary habits can lead to changes in the microbiota, functionally affecting the host nutrition status and immune responses (Kau et al. 2011). For instance, children from The Gambia display growth faltering patterns characteristic of resource poor countries as shown by evidence of cell-mediated enteropathy across a range of nutritional states (Campbell et al. 2003). Despite focused nutrition interventions (e.g. zinc and iron supplementation), growth faltering continues, prompting the need to investigate other EED causal factors.

Exposome Perspectives for EED and Stunting

Children susceptible to under-nutrition suffer from a vicious cycle of diseases, malnutrition, and stunting in low and middle-income countries (Keusch et al. 2013). Given the effects of the microbiome and microbiota on growth and development, there is need to determine the effect of both environmental chemicals on microbes and microbe modifications to environmental chemicals. Our knowledge of the metabolome should be integrated with the gut microbiota of children, both healthy and stunted in EED endemic regions to determine the relationship between host, microbial and dietary derived metabolites and EED (Brown et al. 2015; Ray 2015; Smith et al. 2013; Subramanian et al. 2014). Examining the combined effect of environmental exposures and nutrition in EED animal models and children with EED may also give insights into the basic characteristics of an EED microbiome. Improved understanding of the impact of early-life exposomes on child health is important in the diagnosis, treatment, and prevention of EED (Caricilli et al. 2014). Investigation of the human microbiome, proteome, and metabolome opens up new frontiers for EED research and these approaches should be fully utilized to characterize exposure biomarkers in infancy and childhood. Many studies attempt to show the role of

microbes or microbial effects on EED development (Crane et al. 2015; Keusch et al. 2013), further stimulating discussions about the responsible causal agents. The gut microbiota varies widely between individuals and geographical locations; this may be due to exposome variation in dietary patterns, pathogens, pesticides, drugs, and environmental pollutants. Use of microbial population genetics and metabolomics to describe EED phenotypes across regions is a promising integrative systems biology approach to help discover unknown causes of EED with respect to environmental exposures. For instance, humanized gnotobiotic mice have been used to test the effect of diet, environmental chemicals and toxicants on the gut microbiota and host gastrointestinal physiology (Subramanian et al. 2014; Turnbaugh et al. 2009).

The chronic nature of EED can exacerbate persistent malnutrition and micronutrient deficiencies; hence, there is need to search for new targets for nutritional interventions (McKay et al. 2010). Children in the first 2-years of life have a high likelihood of stunting because of suboptimal breast and complementary feeding practices, micronutrient deficiencies (Barker 2007), poor sanitation and recurrent infections, exposures from mycotoxins, heavy metals and chemical pollutants (Prendergast and Humphrey 2014) as well as exposure to organic pesticides as demonstrated by the presence of their residues in breast milk (Mishra and Sharma 2011; Zhou et al. 2011). The ability for a child to reverse the risk for stunting may be further reduced if not intervened upon in the first 2-years of life as this is a critical window period (Barker 2007), especially if the environment remains resource-constrained or food insecure (Martorell and Zongrone 2012; Prendergast and Humphrey 2014; Victora et al. 2010). This critical window period was demonstrated in a study of healthy Zimbabwe infants where critical periods of poor linear growth were associated with low-grade chronic inflammation (Prendergast et al. 2014). In

addition, specific pathogens or chemical toxicants may aggravate stunting via chronic infections, inflammation, and or gut mucosal damage (Jones et al. 2014).

Nutritional rehabilitation of severely or moderately malnourished children in low income countries should be accompanied by a clear understanding of the impact of diet and environmental toxicants on the overall nutrition profile, and growth and development parameters. There is limited data about the adverse health effects associated with exposure to multiple environmental sources, hence there is need to examine the toxicological effects on the developing GI mucosa and immune systems resulting from cumulative exposures to environmental contaminants (Nweke and Sanders 2009). Geographic information systems (GIS) mapping may be a useful tool in examining the spatial distribution of the exposome in conjunction with other measures. Specifically, EED has been observed alongside stunting in The Gambia, Guatemala, Bangladesh and Malawi (Crane et al. 2015). Using these selected EED research regions, we created a simplified GIS map (Figure 2) demonstrating how variables discussed in this paper (i.e. stunting, chemical exposures and zinc deficiency) illustrate the rationale for further investigation of an EED exposome. Given that the prevalence of low height-for-age (stunting) in children less than 5 years old has been recommended as an indirect indicator of a population's risk for zinc deficiency (Wessells and Brown 2012), additional exposures and exposome identified factors could also be geo-spatially mapped in this context. Correlations between the exposome and EED may lead to novel insights of high relevance to environmental health. With a better understanding of the biomarkers of chemical exposure and EED, we envision a future scenario under which EED can be prevented and treated using multiple approaches that will include a clean living environment, hygiene, better nutrition, and perhaps restored, mature homeostatic gut microbial ecosystems that do not result in growth stunting.

Conclusions and Future Research Needs

The exposome is discussed herein to include a broad spectrum of possible factors that may be involved in EED. This concept offers a novel perspective for chemical toxicants' roles in disrupting microbiota maturity, as chemical toxicants are embedded in the microbial ecosystem and affect how the gut and immune system develop in the first few years of life. Chemical exposures may play a crucial role in early childhood growth and development via multiple mechanisms, and merit inclusion in EED studies across geographically diverse regions. Integration of serum metabolomics and proteomics could reveal an EED-associated exposome across developing nations that could lead to novel and promising approaches to identify, validate and differentiate EED globally. Mechanistic connections between chemical toxicant exposures, immunity and the gut microbiota ecosystem during growth and development may guide future EED therapeutic studies to alleviate stunting. A compelling reason for embracing the exposome in EED is the potential for bidirectional relationships to emerge between biomarkers of exposure and biomarkers of disease, as well as to identify innovative combinations of preventive and therapeutic approaches that can sustainably reduce EED prevalence globally.

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Figure Legends

Figure 1. Environmental exposures that contribute to transient or chronic/persistent EED: A) Conventional factors thought to be responsible for EED; B) Dietary exposure factors known to influence the gut microbiota ecology; C) Environmental toxicants with potential to affect intestinal function and physiology. Dietary exposure and environmental toxicants are emerging factors that can be included in EED associated biomarker identification studies. This classification can help determine the drivers of transient or chronic EED states.

Figure 2. Observations of stunting, obsolete chemical stockpiles and zinc deficiency in five environmental enteric dysfunction research regions: Guatemala, Malawi, The Gambia, Bangladesh and Nepal. This simplified GIS map shows two variables from the exposome, namely chemical pesticides and zinc deficiency, and associations in known EED affected countries alongside stunting. Data source for stunting: The World Health Organization, updated 2014. Data source for obsolete chemical stockpiles: Food and Agriculture Organization of the United Nations (last accessed 2015). Data source for Zinc deficiency: Wessells & Brown 2012.

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Figure 1.

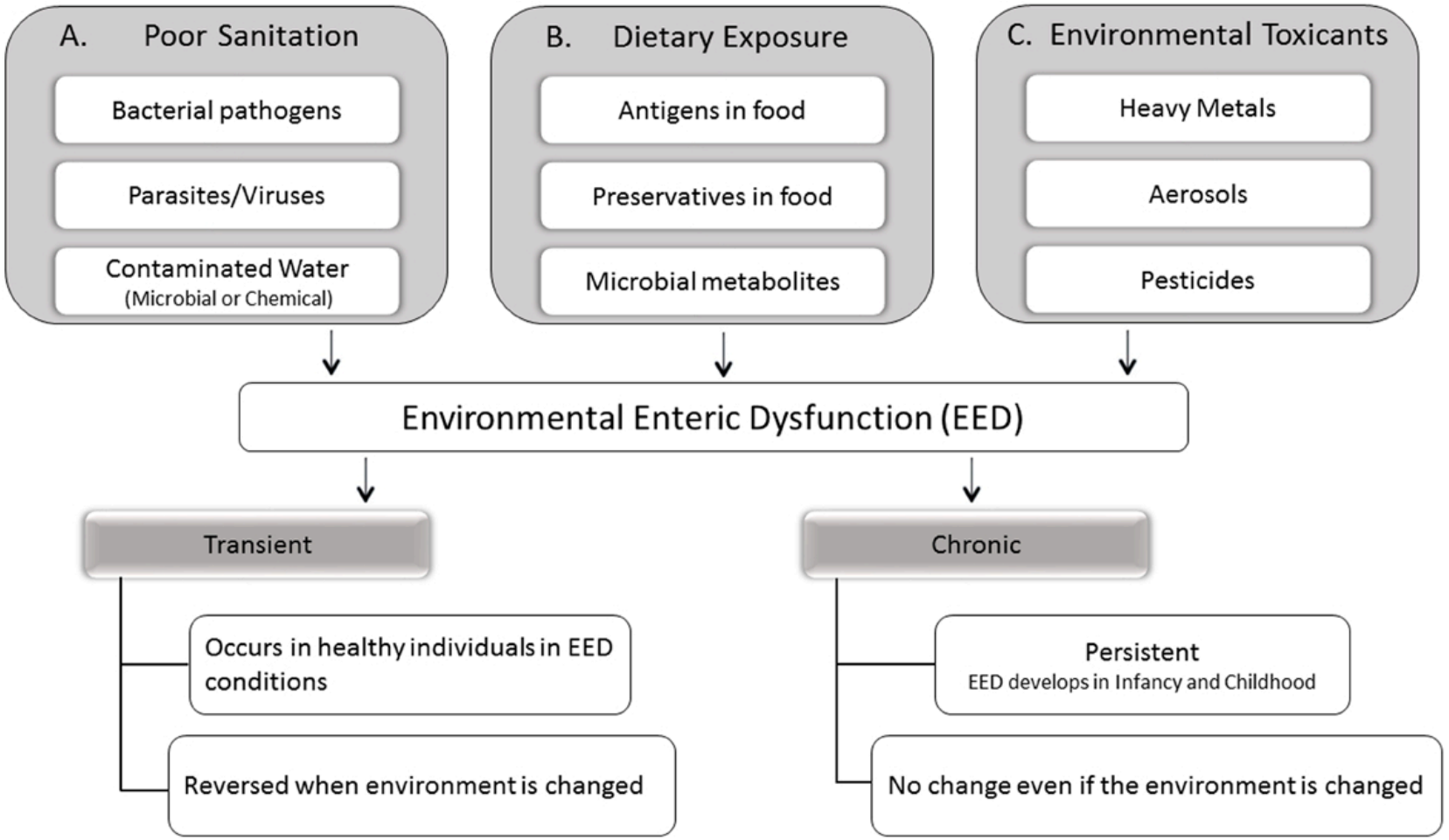
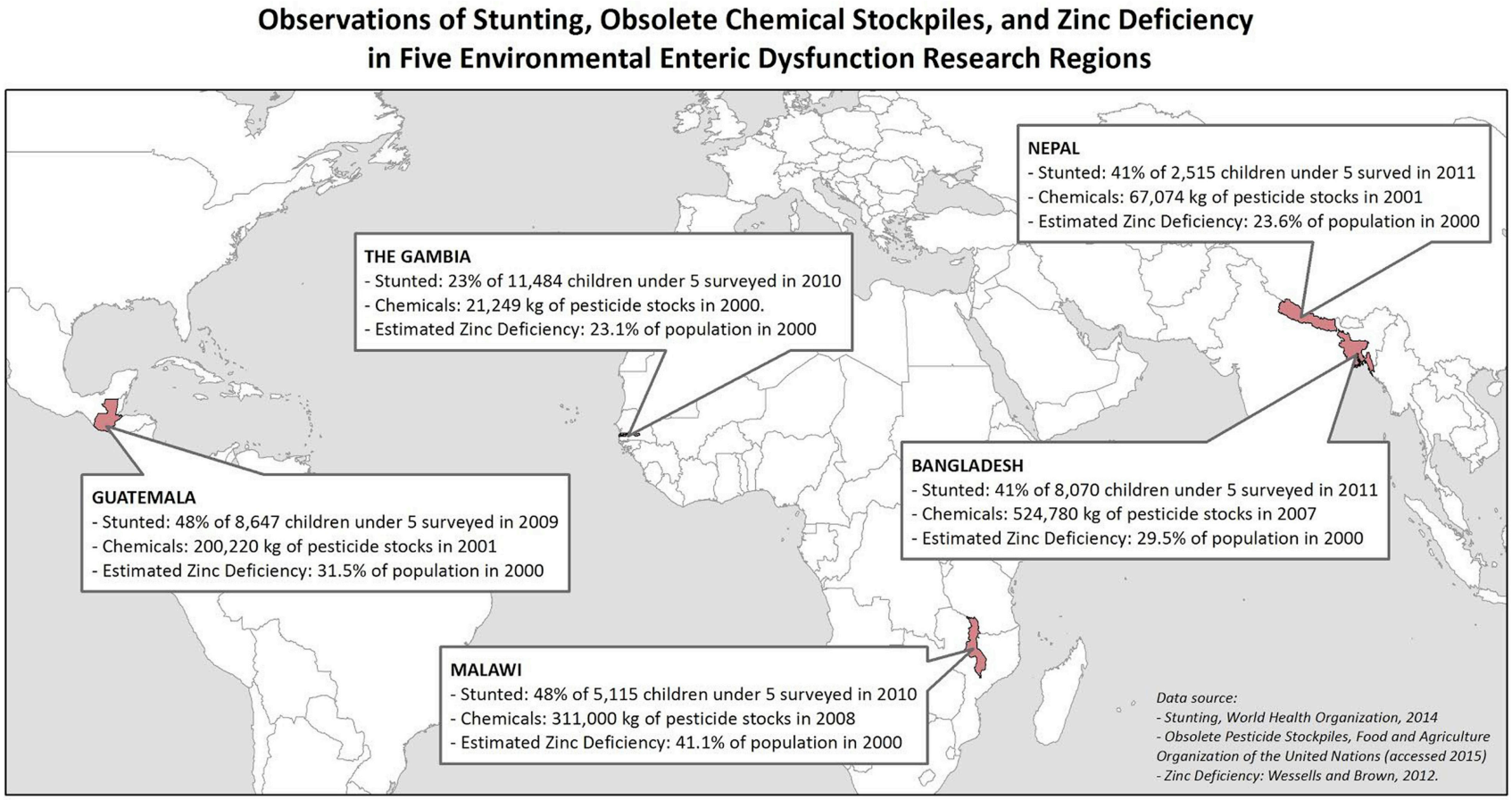


Figure 2.


Observations of Stunting, Obsolete Chemical Stockpiles, and Zinc Deficiency in Five Environmental Enteric Dysfunction Research Regions
NEPAL
- Stunted: 41% of 2,515 children under 5 served in 2011
- Chemicals: 67,074 kg of pesticide stocks in 2001
- Estimated Zinc Deficiency: 23.6% of population in 2000
THE GAMBIA
- Stunted: 23% of 11,484 children under 5 surveyed in 2010
- Chemicals: 21,249 kg of pesticide stocks in 2000.
- Estimated Zinc Deficiency: 23.1% of population in 2000
BANGLADESH
- Stunted: 41% of 8,070 children under 5 surveyed in 2011
- Chemicals: 524,780 kg of pesticide stocks in 2007
- Estimated Zinc Deficiency: 29.5% of population in 2000
GUATEMALA
- Stunted: 48% of 8,647 children under 5 surveyed in 2009
- Chemicals: 200,220 kg of pesticide stocks in 2001
- Estimated Zinc Deficiency: 31.5% of population in 2000
MALAWI
- Stunted: 48% of 5,115 children under 5 surveyed in 2010
- Chemicals: 311,000 kg of pesticide stocks in 2008
- Estimated Zinc Deficiency: 41.1% of population in 2000
Data source:
- Stunting, World Health Organization, 2014
- Obsolete Pesticide Stockpiles, Food and Agriculture Organization of the United Nations (accessed 2015)
- Zinc Deficiency: Wessells and Brown, 2012.